Utility of polygenic scores in healthcare

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POLYGENIC RISK SCORES (PRS)/ POLYGENIC SCORES (PGS)

- What are they, what do they measure?
- Why interesting?
- Public perception
- Examples of their possible use in healthcare
- Validity versus utility

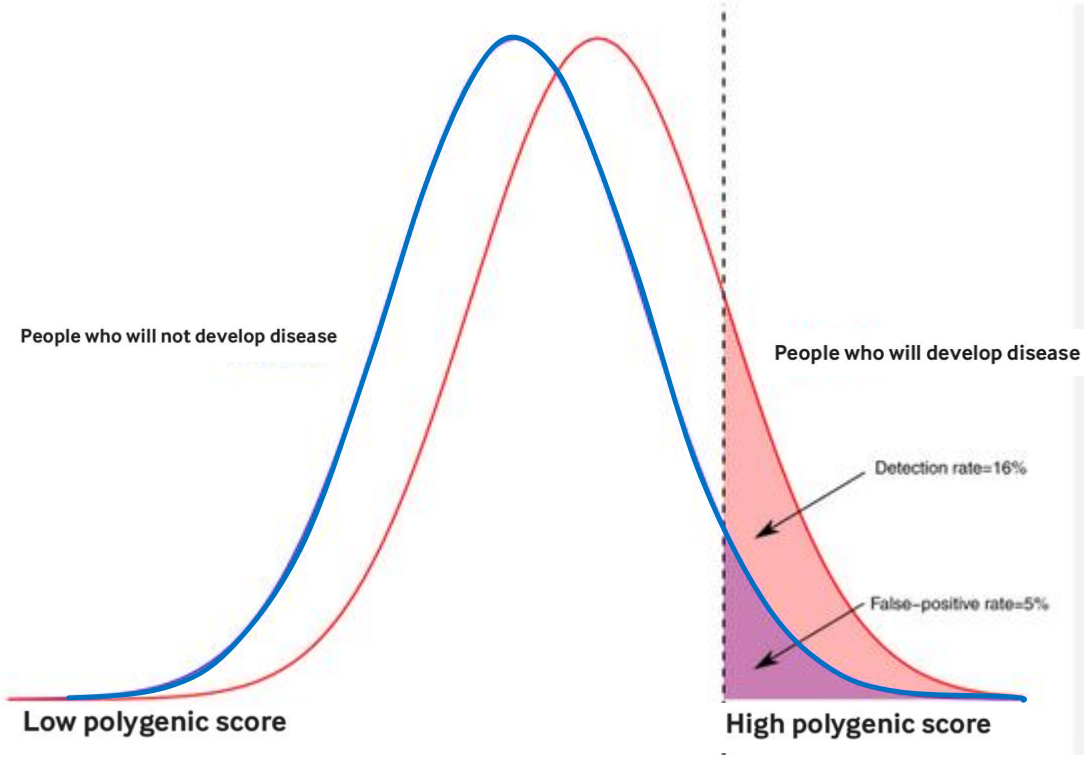
WHAT ARE POLYGENIC RISK SCORES?

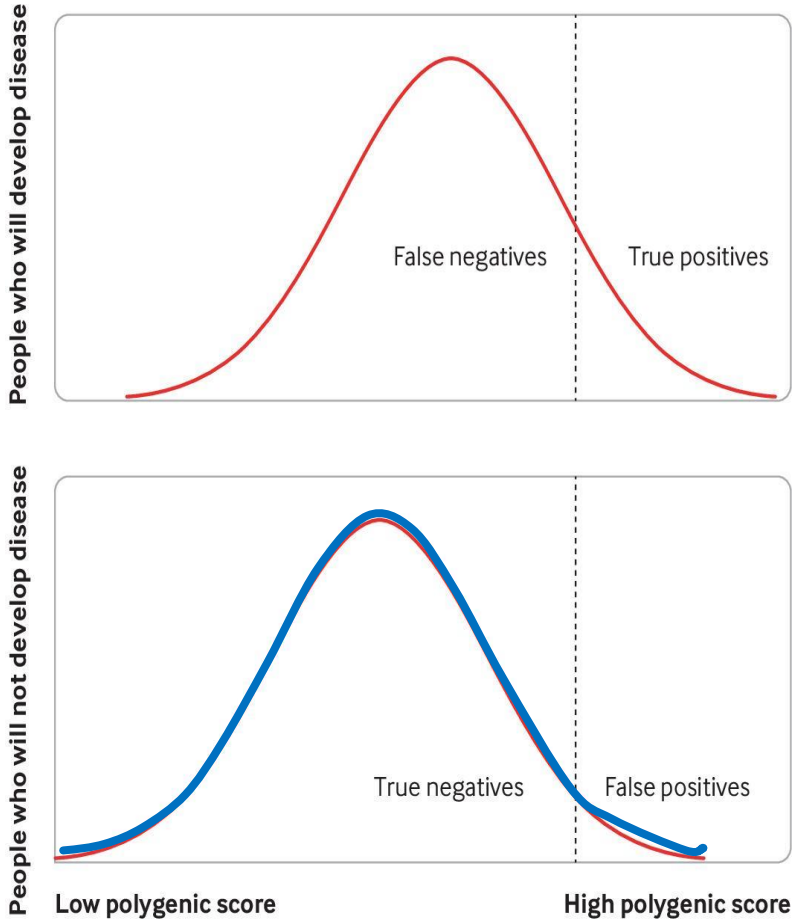
- PRS amalgamate the effects of thousands of common genetic variants identified through GWAS.
- These variants individually have minor impacts on disease risk, but collectively they enable an assessment of susceptibility to common multifactorial diseases such as heart disease and cancer.

Note:

- Different to rare variants of common diseases (eg BRCA, Lynch, familial hypercholesterolaemia) where a few genetic variants often dominate a risk profile.
- They describe the genetic component of multifactorial diseases, not the other components. Socio-demographic/ lifestyle/ random factors may represent bulk of risk

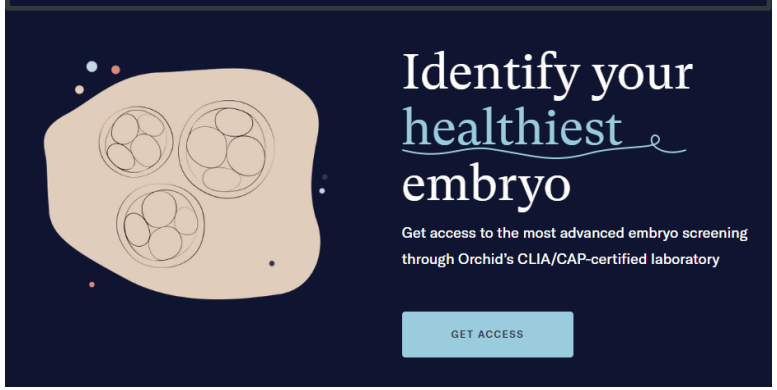
Choosing thresholds for declaring a “high” polygenic score.





PROMISSORIES SURROUNDING PRS

Preimplantation screening using PRS for common adult onset diseases



UK Secretary of State for Health 2019

"my risk of prostate cancer by the age of 75 is high [almost 15%]...the truth is this test may have saved my life"

"These tests are useful and cost effective…what if we could rule out colon cancer for most people with a simple test and then identify the small number of people who need a colonoscopy"

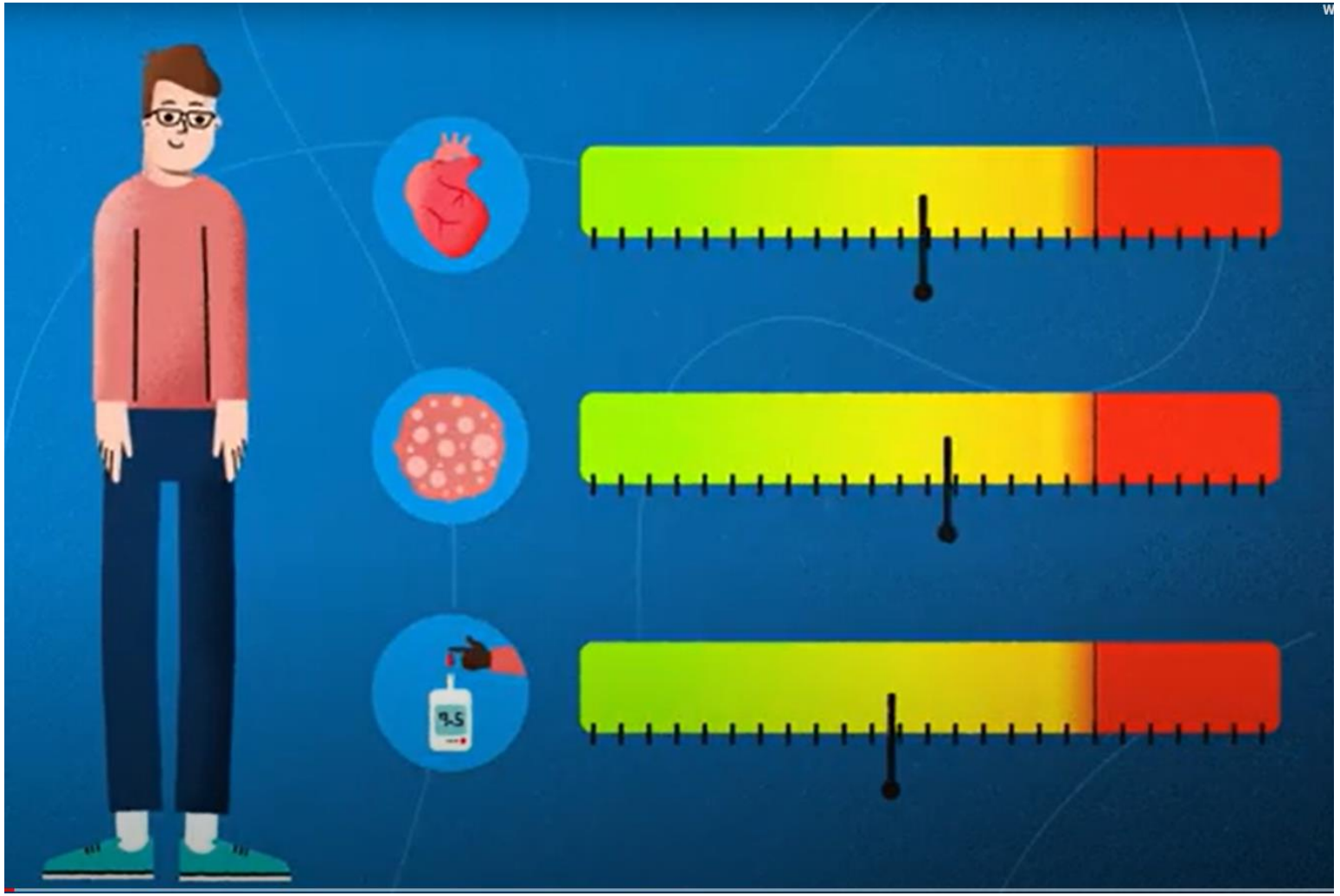
+ Our Future Health

In partnership with NHS

"We can change the whole paradigm of healthcare [through PRS"]

"Identify those at increased risk and match them to the right screening pathway"

POLYGENIC RISK SCORES- CPM ANIMATION



"Imagine you knew you were at high risk of developing a heart attack? That's pretty clear motivation to do something about it…
How would you know?....
A major risk factor for common diseases is our own genetic code…."

BUT…

- For most of these diseases, polygenic scores contribute around 20% of total risk.
- So knowing whether high or low polygenic risk may say relatively little about absolute risk of disease

Cancer	RR between top and bottom 5%	AUC	Average lifetime risk (%)	Lifetime risk at 95th percentile (%)	Detection rate (%)	False positive rate (%)
Prostate	15	0.67	13	31	16	5
Breast	9	0.63	13	27	13	5
Colorectal	6	0.61	4	7	11	5
Pancreatic	5	0.60	2	4	10	5
Ovarian	4	0.57	2	3	9	5

RISK COMMUNICATION

Notoriously difficult

- Be clear about absolute risks:

  Eg top 5% of polygenic scores for

Colorectal cancer –lifetime risk of 7% (population risk ~4%)

Ovarian cancer, lifetime risk 2.1%, (population risk of 1.6%)

- "High risk" may want clinical discussion "low risk" might be less likely to seek medical attention
- Top 1% has potential to be clinically useful (eg breast cancer- approaching *BRCA1/2* level risks) but then not useful in 99%

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Realistic expectations are key to realising the benefits of polygenic scores

We must not let enthusiasm around polygenic scores allow us to forget other factors that are bigger, more modifiable, and relevant for everyone, argue Amit Sud, Rachel Horton, and colleagues

Amit Sud,[1,2] Rachel H Horton,[3,4,5] Aroon D Hingorani,[6,7,8,9] Ioanna Tzoulaki,[10,11,12] Clare Turnbull,[1,13] Richard S Houlston,[1] Anneke Lucassen[4,5,14]

Key messages

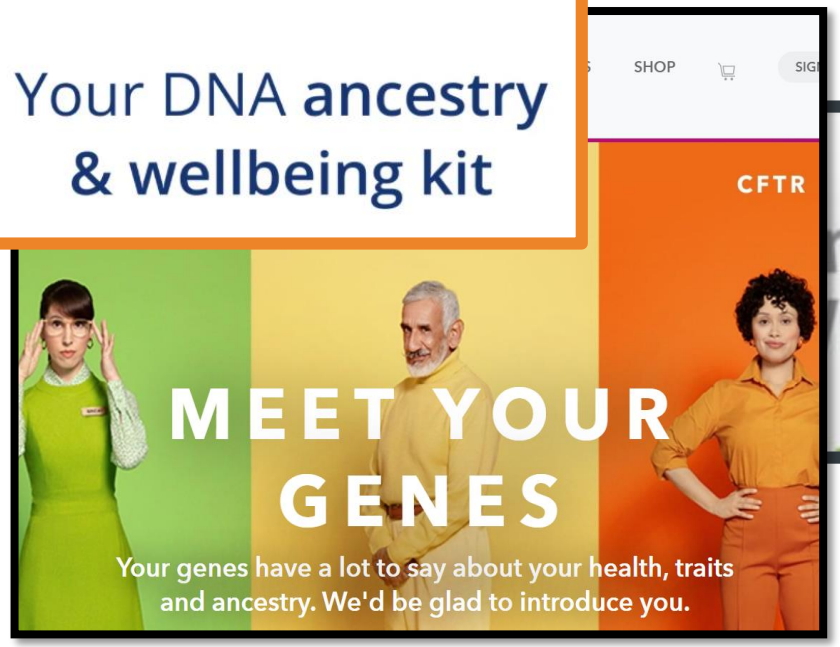
- Polygenic scores will always be limited in their ability to predict disease, as much of a person's disease risk is determined by factors that polygenic scores cannot measure
- If we do not effectively communicate this limitation, we risk overemphasising the role of polygenic scores, which could undermine current effective screening programmes
- The enthusiasm around polygenic scores must not distract from efforts to tackle modifiable risk factors for disease

Amid the hope that polygenic scores will "change the whole paradigm of healthcare,"[5] we should recognise that these scores are limited in their potential to predict disease. If we do not set our expectations accordingly, they could harm rather than help.

Polygenic scores will always be limited in their ability to predict disease

Polygenic scores offer the possibility of assessing a person's genetic risk for multiple diseases simultaneously, at any point in their life course. But they do not consider the effects of environmental or

EXPECTATIONS INFLUENCED BY DTC APPROACHES



WHAT MIGHT PEOPLE EXPECT FROM POLYGENIC SCORES?

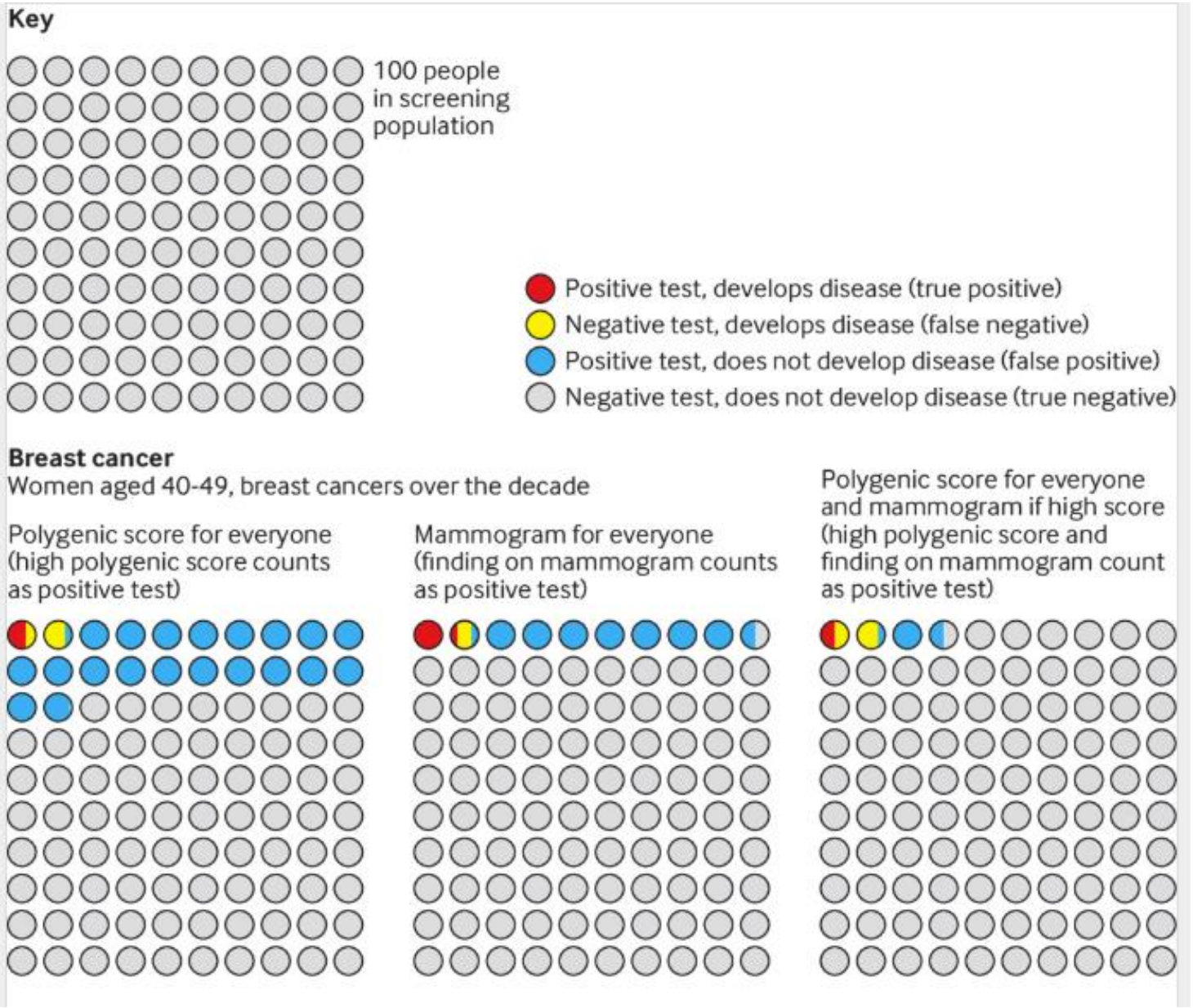
Discourses around genetics remain deterministic- expectation that if only the technology improves, clear findings will leap out from the genetic code

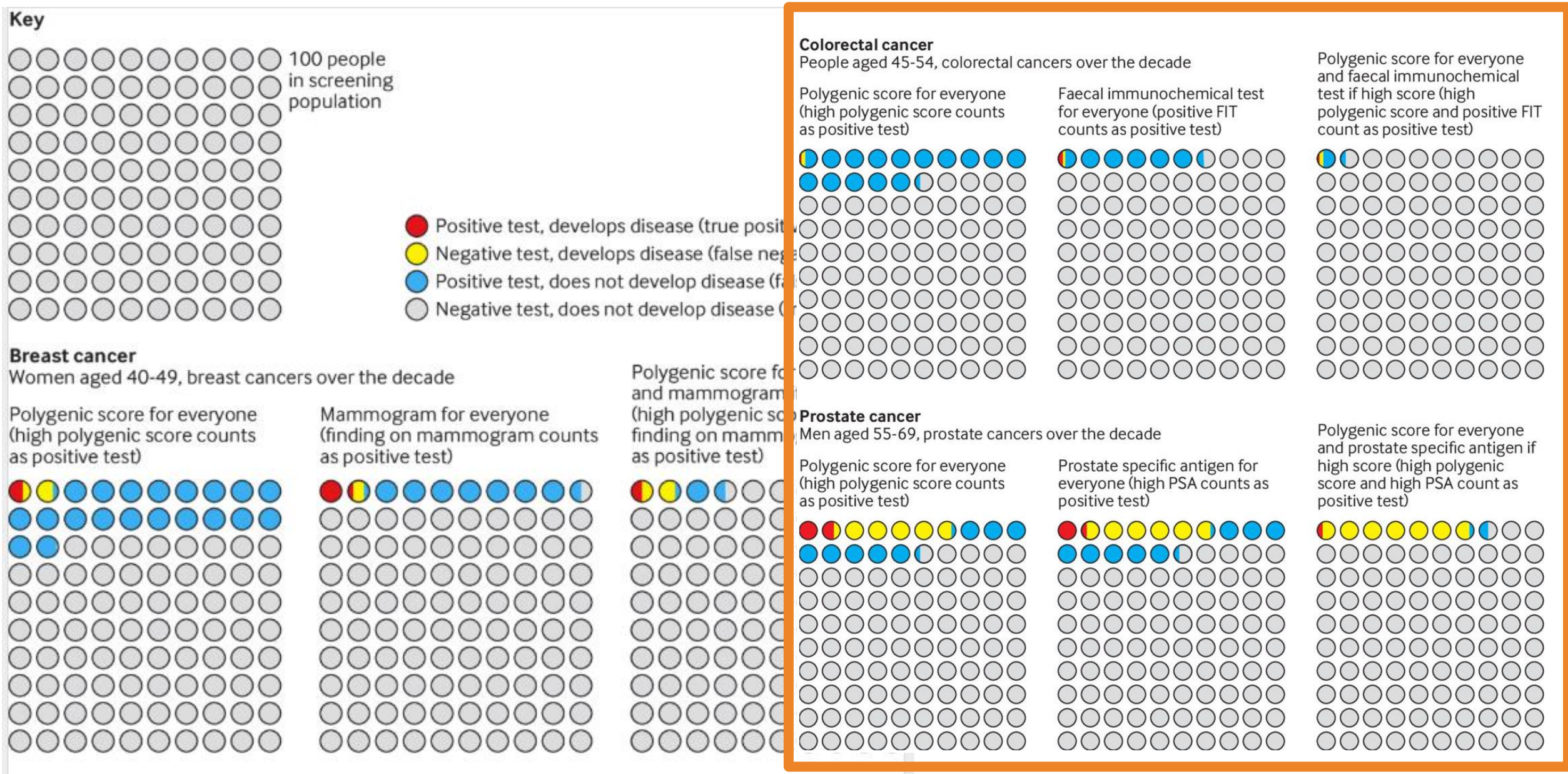
Unlike other factors that might subtly nudge a person's risk one way or another, people might read more into "genetic" tests

PPIE group: if we call them polygenic *risk* scores assume they say something clear about risk

PPIE DISCUSSIONS

- Will always be limited in their ability to predict who will get a disease and who will not, as so much of a person's disease risk is determined by factors that polygenic scores cannot measure.
- It is not intuitive (and potentially counter to people's expectations) that polygenic scores only measure a small component of overall disease risk.
- If we do not effectively communicate this limitation, we set ourselves up for overinterpretation of polygenic scores (leading to unnecessary resource use to mitigate perceived 'high risk', or under investigation and inappropriate reassurance of people thought to be at 'low risk'), which could undermine current effective screening programmes (eg bowel cancer screening through FIT testing).


Key
100 people in screening population
Positive test, develops disease (true positive)
Negative test, develops disease (false negative)
Positive test, does not develop disease (false positive)
Negative test, does not develop disease (true negative)
Breast cancer
Women aged 40-49, breast cancers over the decade
Polygenic score for everyone (high polygenic score counts as positive test)
Mammogram for everyone (finding on mammogram counts as positive test)
Polygenic score for everyone and mammogram if high score (high polygenic score and finding on mammogram count as positive test)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Colorectal cancer
People aged 45-54, colorectal cancers over the decade
Polygenic score for everyone (high polygenic score counts as positive test)
Faecal immunochemical test for everyone (positive FIT counts as positive test)
Polygenic score for everyone and faecal immunochemical test if high score (high polygenic score and positive FIT count as positive test)
Prostate cancer
Men aged 55-69, prostate cancers over the decade
Polygenic score for everyone (high polygenic score counts as positive test)
Prostate specific antigen for everyone (high PSA counts as positive test)
Polygenic score for everyone and prostate specific antigen if high score (high polygenic score and high PSA count as positive test)

EXAMPLE IN CARDIOVASCULAR DISEASE

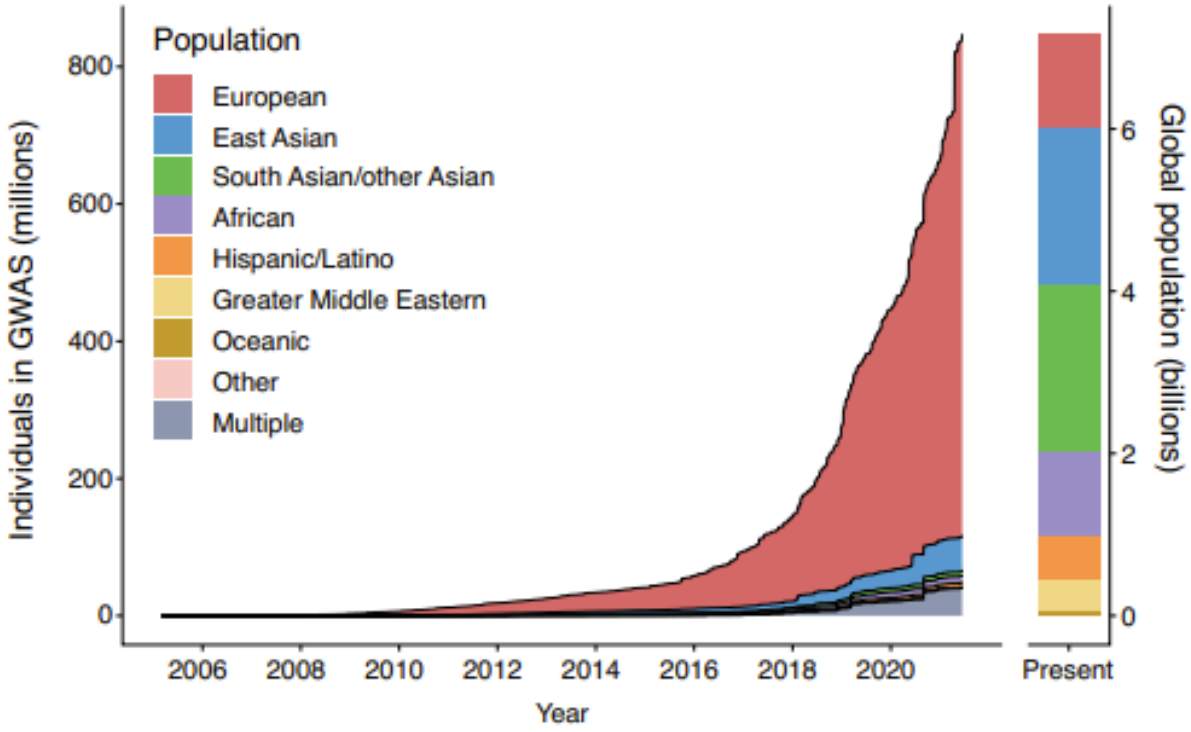
- Screen 100,000 people using conventional risk factors +/- PRS
- With a 10% ten year risk cut-off (current indication for statins) the number needed to genotype to find an additional case was 1149
- Number needed to genotype to prevent an additional CVD event was 5882
- Offering all those over 40 years statins gives number needed to treat to prevent CVD of 63
- Recent cost analysis suggested $140,000 per QALY for PRS (but only incorporated technical costs)

SUBSEQUENT INTERVENTION IMPORTANT

- Screening programme requires detection at an earlier point than symptomatic, *and* where a subsequent intervention will change the course of the disease
- Problem in eg prostate cancer screening- PRS detect mainly indolent cancers which would not affect survival but their detection may cause anxiety and uncertainty about definitive treatment
- Important to find PRS that predict disease progression rather than onset
- Age as proxy for PRS- unlike most biomarkers PRS fixed at conception, so can be measured then. But limited utility of knowing increased (or decreased) risk several decades before any intervention can be offered.
- Beware preconception/ newborn PRS

DIVERSITY IN GENOMICS AND BIAS

- Despite calls to improve diversity in genomic research, global collections remains overwhelmingly Eurocentric
- Understanding of clinical effects of genetic variation good in European ancestries.
- Polygenic scores developed on European GWAS: Scores have lower predictive accuracy when applied to people with non-European ancestry. Risk of widening inequities



FOR DISCUSSION

- Consider the population in which PRS designed: currently PRS set to benefit people with European ancestry more than anyone else. *Many attemps to* recruit a diverse range of people to studies such as OFH, but it is important to remember that at present, where polygenic scores work, they may widen gaps and worsen inequities.
- For most common diseases, unglamorous but well established risk factors like smoking, obesity, and socioeconomic deprivation matter more than a person's genetic background.
- NHS aiming for net-zero healthcare (Karliner et al. 2023), and mass genetic testing is likely to have a significant carbon footprint. Is environmental cost sufficiently offset by the clinical and other benefits?

UTILITY OF POLYGENIC RISK

Debate at the centre for personalised medicine (CPM) Oxford 18th April 2023:

https://cpm.ox.ac.uk/watch-our-lectures-interviews/

Amit Sud: https://cpm.ox.ac.uk/lecture/polygenic-risk-scores-and-cancer-dr-amit-sud/

Aroon Hingorani: https://cpm.ox.ac.uk/lecture/polygenic-risk-scores-and-cardiovascular-disease-professor-aroon-hingorani/

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